American Journal of Hematology 58:87–90 (1998)

$DAB_{389}IL2$ Diphtheria Fusion Toxin Produces Clinical Responses in Tumor Stage Cutaneous T Cell Lymphoma

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Four patients with late stage cutaneous T cell lymphoma (IB-IVA) who had failed at least two previous therapies were treated with $DAB_{389}IL2$ at 9 or 18 μg/kg as 15-min intravenous infusions daily for 5 days every 3 weeks for eight cycles. Mild vascular leak syndrome (VLS) with transient edema, hypoalbuminemia, weight gain, and myalgias was observed in two of the patients lasting 7–10 days and only occurring on the first cycle. One stage IB patient had a pathologic complete remission (CR) lasting 11+ months from treatment initiation, one stage IIB patient had a complete clinical remission (CCR) lasting >6 months with complete clearing of a large tumor lasting >18 months, and one stage IIB and the one stage IVA patient had partial remissions (80–99% reduction in tumor masses) lasting 5 months. While IL2 receptor (IL2R) was expressed on 20–50% of tumor cells prior to therapy, recurrent tumor was IL2R negative in three of the patients. $DAB_{389}IL2$ at tolerable doses decreased tumor burden in each of these four standard treatment refractory CTCL patients and may offer an important alternative to standard palliative chemotherapy regimens. Am. J. Hematol. 58:87–90, 1998.

Key words: $DAB_{389}IL2$; cutaneous T cell lymphoma (CTCL); topical therapies; IL2R

INTRODUCTION

Tumor stage CTCL lesions are composed of clonal malignant T helper lymphocytes that may extend from epidermis to deep subcutaneous tissues [1]. Topical therapies including nitrogen mustard ointment, PUVA, and electron beam radiotherapy penetrate poorly, and, consequently, fail to provide palliation [2]. While α-interferon and cytotoxic chemotherapy are active in tumor stage CTCL [3], the delivery of these treatments is complex, time-consuming, and associated with multiple adverse effects. Further, efficacy is variable and responses are usually of only a few months' duration. Based on these results, we sought unique molecular targets on tumor stage CTCL cells, which could be used to selectively target toxic compounds. The high affinity IL2R, a heterotrimer composed of α, β, and γ subunits, binds IL2 with a Kd of 10^{-12} M [4]. IL2R is expressed on activated T cells, B cell, and monocytes, but no other normal human tissues [4]. Approximately, half of CTCL patients express IL2R on their abnormal lymphocytes [5]. We employed a diphtheria fusion toxin, $DAB_{389}IL2$, consisting of the first 389 amino acid residues of diphtheria toxin (DT) with the catalytic and translocation domains fused to the 133 amino acid residue IL2 peptide [6]. In a phase I study, $DAB_{389}IL2$ was systemically infused in patients with hematologic malignancies [7]. The maximal tolerated dose was 18 μg/kg/day for 5 days every 3 weeks. Dose-limiting toxicities were transiently elevated hepatic transaminases, flu-like symptoms with fever, nausea, vomiting, rash, and headaches, and mild vascular leak with hypotension and hypoalbuminemia. Patients with IL2R α expression and CTCL were more likely to respond.

PATIENTS AND METHODS

Based on these results, patients were entered into a phase II protocol if they gave signed informed consent, had histopathologic confirmation of CTCL with immunohistochemical presence of IL2R on ⩾20% of tumor

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Received for publication 12 November 1997; Accepted 10 December 1997

TABLE I. Characteristics of CTCL Patients Receiving $DAB_{389}IL2$*

Patient No.	Age (years)	Sex	Stage	Duration (years)	Previous therapy	%BSA	CD25 (%)	Dose (μg/kg)	Toxicities	Decrease tumor burden (%)	Response/ time to best response (months)	Duration (months)
1	26	F	IVA	2	I,R	88	20	18	SOB	68	PR/3	5
2	63	M	IIB	10	I,R,C,P,N,S,T	20	50	18	Pain	100	CCR/4	6+
3	56	F	IB	3	P,N,T,C,Y	22	20	9	None	100	CR/1	11+
4	58	F	IIB	3.5	N,I,P	17	50	18	VLS	100	PR/1	6

*I = alpha interferon; R = 13-cis-retinoic acid; C = CHOP combination chemotherapy; P = PUVA; N = topical nitrogen mustard; S = steroids; T = total skin electron beam radiotherapy; Y = thymopentin; SOB = shortness of breath; VLS = vascular leak syndrome; PR = partial remission; CCR = complete clinical remission; CR = pathological complete remission. A complete remission is indicated by no evidence of disease by tumor burden assessments, photography, and histopathology. A partial remission is a >50% reduction in measured tumor burden compared to baseline.

cells, had stage IB-IVA disease and had received ⩾4 previous therapies for stage IB-III disease or ⩾1 previous therapy for IVA disease with evaluable disease in skin, blood, or nodes, were out ⩾14 days from anti-cancer therapy, were on no topical steroids and had no active systemic infections including HIV, HTLV-1, hepatitis B or C, had no cardiac/pulmonary/renal/CNS/hepatic/hematologic dysfunction, had no other malignancies at baseline, and had an ECOG performance status of 0–2. Treatment consisted of premedication with 650 mg acetaminophen and 25 mg diphenhydramine followed by 9 or 18 μg/kg $DAB_{389}IL2$ intravenous infusions over 15 min daily for 5 days every 21 days for eight cycles. Patients were monitored with weekly chemistry profiles, CBC, urinanalysis, and physical examinations. The NCI common toxicity criteria used was modified to add scores for hypoalbuminemia (grade I, 2.9–3.4 g/dl; grade II, 2.4–2.8 g/dl; grade III, 2–2.3 g/dl; grade IV, ⩽2 g/dl). Anti-DT titers were obtained prior to each course and at final evaluation. Clinical disease assessments were done before each course and included a weighted skin/erythroderma involvement-extent severity index [8] (with a weighting of 1 for patch, 2 for plaque, and 3 for tumor/ulcer lesions) and measurement of 1–5 skin lesions and nodes. Patients underwent rebiopsy of skin lesions at the time of study discontinuation for evaluation of CTCL histopathology and IL2R expression. Four patients with advanced CTCL accrued at our institutions on the protocol serve as the basis of this report.

RESULTS

Four patients with advanced tumor stage CTCL who had been previously refractory to conventional therapies are presented in Table I. The mean age was 51 years old, and there were three females and one male. The main symptom and finding were skin tumors and plaques involving on average 36% of the body surface area. Patients had previously failed an average of four therapies. IL2R expression measured by immunohistochemistry on lesions from each of the patients varied from 20–50%. Three patients received 18 μg/kg/day, and one patient received 9 μg/kg/day.

The clinical responses are shown in Figure 1 and Table I. There was one pathologic complete remission, one clinical complete remission with histologic improvement, and two partial responses. The duration of response ranged from 3–10+ months. Of importance is the markedly improved quality of life in these patients undergoing regression of their disfiguring and painful skin lesions. With few symptoms from treatment and skin improvement, all of the patients were able to participate in normal life activities. Interestingly, responses were seen soon after initiation of treatment with most of the tumor regression occurring after the first or second course.

Side effects during therapy did occur. Patient no. 1 experienced transient wheezing and severe shortness of breath during the second dose of cycle 6 and discontinued further therapy. Patient no. 2 had severe pain in his large thigh tumor followed by ulceration after the first infusion of $DAB_{389}IL2$, which improved with shrinkage of the tumor. Patient no. 3 did not have symptoms during treatment courses. Patient no. 4 experienced vascular leak syndrome after the first cycle with hypotension, edema, hypoalbuminemia, weakness, fevers, and nausea lasting for 1 week and slowly resolving without therapy. The syndrome did not recurr on later cycles. Humoral antibody against DT was detected in all patients after the first cycle.

DISCUSSION

$DAB_{389}IL2$ was well tolerated by these four patients at 9 and 18 μg/kg and was associated with one vascular leak episode and one allergic-type bronchospasm event. The low incidence of toxicities may have been due in part to the significant tumor burden in most patients acting as an ''antigen sink'' as has been observed in other immunotoxin trials [9]. The relatively short plasma half-life (30 min) may have also reduced exposure of vascular endothelium to toxic concentrations of drug. Increased

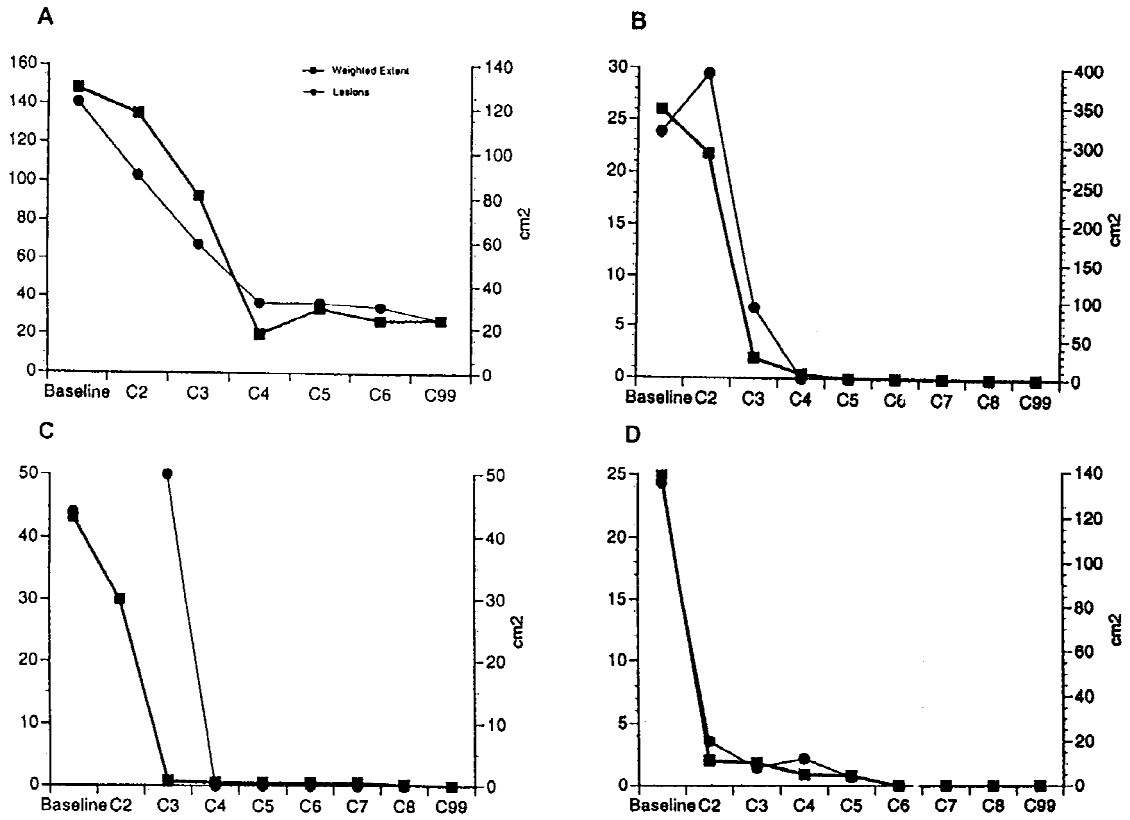

Fig. 1. Weighted skin extent severity assessments and tumor size measurements for patients during study. A: Patient no. 1. B: Patient no. 2. C: Patient no. 3. D: Patient no. 4. ●, weighted skin extent severity assessment score as described in Patients and Methods; ■, tumor size measured on sentinel lesions in cm².

vascular leak syndrome has been observed upon modification of the circulating half-life of other immunotoxins such as by deglycosylation of ricin A chain [9]. Immunosuppression was not seen, and patient no. 1 was treated without complication with intercurrent staphylococcal and candidal sepsis. This observation was not unexpected, since the toxin is targeted only to IL2R expressing cells, which constitute a small percentage of patient T and B lymphocytes [4]. In fact, the absence of myelosuppression in these patients suggests the drug is safer and better tolerated than chemotherapy in these patients with disease-induced breakdown in the skin barrier to microorganisms.

DAB$_{389}$IL2 appears to produce rapid responses in sensitive patients. Most of the reductions in tumor burden occurred by the third cycle. The rapid rate of response suggests a direct protein synthesis inhibition and apoptosis of target cells rather than an immunologic mechanism. The IL2Rα density, initial tumor burden, age, sex, number or type of prior therapies, antibody titers, and presence or absence of toxicities failed to predict for the degree of response among these four patients. In vitro tumor cell sensitivity to DAB$_{389}$IL2 depends upon the presence of α, β, and γ IL2R subunits is poorly predicted by IL2R α alone [10]. The lack of effect of anti-DT antibodies on efficacy may be due to the predominant role of the binding domain epitopes in toxin neutralization [11]. In each of these four patients, their lifestyle changed from home confinement and continuous pain and depression to a more active life with social interaction and, in several of the cases, return to work. The observation that DAB$_{389}$IL2 had dramatic and durable anti-tumor activity in these four patients, suggests that the drug may be an important new therapeutic tool for treatment refractory, advanced stage CTCL.

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